REMARKS

In the Office Action dated October 21, 2004, the Office allowed claims 1-44.

Rejection Under 35 U.S.C. § 103(a)

The Office rejected claims 60-67 and 81-91 under 35 U.S.C. § 103(a) as being unpatentable over applicant's admissions in view of Krushinski, Jr. et al. (5,576,321). More specifically the Office stated that "In this application the skilled artisan would have been to combine olanzapine with known compounds that are serotonin reuptake inhibitors and mixed serotonin-norepinephrine reuptake inhibitors to treat psychotic disorders since each is known to treat psychotic disorders."

Whether claims 60-67 and 81-91 are unpatentable under 35 U.S.C. § 103(a) in view of Krushinski, Jr. et al, depends upon whether the differences between the subject matter sought to be patented and the prior art, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains, not whether it would have been obvious to one skilled in the art to try various combinations of old elements. Changes from the prior art must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make the changes that would produce the claimed invention.

In 1995 it was reported by Preskorn and Lacey that even though understanding of the clinically relevant pharmacodynamics and pharmacokinetics of psychotropic medications had developed substantially over the last 40 years, the rational use of copharmacy was still hampered by a lack of systematic research. [Preskorn and Lacey, *Journal of Practical Psychiatry and Behavioral Health*, 92-98 (July 1995) referred to hereinafter as "Preskorn". See in particular page 92, second column] Copharmacy as defined therein is the intentional, concomitant use of two medications. [See Preskorn, page 92, second column, third paragraph, third sentence]

Preskorn provides a Table 2 outlining 12 criteria to be considered for rational copharmacy in psychiatry. [See Preskorn, page 94, second column] These 12 criteria are:

1. Knowledge that the combination has a positive effect on the pathophysiology or pathoetiology of the disorder.
2. Convincing evidence that the combination is more effective, including more cost-effective, than monodrug therapy.

3. The combination should not pose significantly greater safety or tolerability risks than monotherapy.
   a. Drugs should not have narrow therapeutic indices.
   b. Drugs should not have poor tolerability profiles.
4. Drugs should not interact both pharmacokinetically and pharmacodynamically.
5. Drugs should have mechanisms of action that are likely to interact in a way that augments response.
6. Drugs should have only one mechanism of action.
7. Drugs should not have a broad-acting mechanism of action.
8. Drugs should not have the same mechanism of action.
9. Drugs should not have opposing mechanisms of action.
10. Each drug should have simple metabolism.
11. Each drug should have an intermediate half-life.
12. Each drug should have liner pharmacokinetics.

Of particular note, Preskorn states on page 96, first column, third paragraph, the following with regard to criteria 4:

"Examples of drugs that can produce both pharmacokinetic and pharmacodynamic interactions include some SSRIs (e.g., fluoxetine), which inhibit one or more P450 enzymes in addition to their intended effect on the serotonin uptake pump... In general, the use of such drugs as part of a copharmacy strategy should be avoided, because the outcome could be due to either a pharmacodynamic or pharmacokinetic interaction." (emphasis added)
In addition, referring specifically to fluoxetine, Preskorn states on page 96, second column, first paragraph, that:
"Fluoxetine is the most problematic of all the SSRI's to use in copharmacy..."
Moreover, Preskorn states in the same paragraph that:
"Because fluoxetine follows nonlinear pharmacokinetics, the magnitude and the duration of these effects are increased in a nonlinear fashion with dose increases. Taken together, these factors make copharmacy with this drug particularly complicated." Applicants respectfully assert that the above teachings direct one of ordinary skill in the art away from the present invention.

In addition, Preskorn states with regard to criteria 6 on page 97, first column, 4th paragraph:

"The more mechanisms of action that each drug in the combination has, the more likely that there will be an increase in either safety or tolerability problems and the more ways the drugs can interact pharmacodynamically."

In view of the above statement, Applicants wish to point out that one of ordinary skill in the art would appreciate that olanzapine possesses a rich pharmacology with affinity for numerous neurotransmitter receptors, such as serotonin ($5HT_{2A}$, $5HT_{2C}$, $5HT_3$), dopamine (D_1, D_2, D_4), histamine H_1, α_1-adrenergic, and muscarinic receptors. [See for example F.P. Bymaster, et al., *Neuropsychopharmacology*, 14(2), 87 (1996)] One of ordinary skill in the art would further appreciate that such a rich pharmacology could provide for multiple potential mechanisms of therapeutic action. Hence, Applicants assert that the above statement by Preskorn in combination with the knowledge of one of ordinary skill in the art regarding the broad pharmacological profile of olanzapine provides further support for a teaching away from the present invention.

Moreover, Preskorn points out on page 97, first column, 5th paragraph, with regard to criteria 7, that even though a drug may have only one mechanism of action, that action may have wide ranging effects on brain function, such as selective serotonin reuptake inhibitors (SSRI's, e.g. fluoxetine) which affect all presynaptic serotonin terminals. That is, drugs should not have a broad-acting mechanism of action. Thus, again, Preskorn teaches away from the present invention.

Applicants take note that the Office has referred to In re Kerkhoven for support of the above-cited rejection of claims 60-67 and 81-91. In particular, the Office indicated that In re Kerkhoven states that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is to be used for the very same purpose." [In re Kerkhoven, 205 USPQ 1069 (CCPA 1980)]. However, Applicants respectfully submit that In re Kerkhoven is related to a combination of detergents, not the combination of drugs for use in a complex and highly variable biological system, such as a human being, where, as Preskorn discloses, many variable factors need to be considered. Hence, Applicants respectfully assert that the analysis in In re Kerkhoven is inapposite to the present invention.

In view of the above, Applicants respectfully assert that the prior art does not suggest, much less teach the inventions covered in rejected claims 60-67 and 81-91. At best the prior art makes the present invention "obvious to try". However, Applicants assert that "obvious to try" is not the standard by which obviousness under 35 U.S.C. 103(a) is determined. Furthermore, Applicants assert, that in view of the numerous teachings of Preskorn

specifically set forth above, that Preskorn, teaches one of ordinary skill in the art away from the present invention. Thus, Applicants respectfully assert that rejection of claims 60-67 and 81-91 under 35 U.S.C. § 103(a) as being unpatentable in view of Krushinski, Jr. et al., is improper.

Rejection Under The Judicially Created Doctrine of Obviousness-Type Double Patenting

The Office rejected claims 60-64 and 81-85 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,147,072.

While Applicants do not necessarily agree with the Office's assessment of claims 60-64 and 81-85 under the obviousness-type double patenting rejection, Applicants provide, only in order to expedite prosecution, a Terminal Disclaimer pursuant to 37 C.F.R § 1.321. Applicants further submit that the filing of this Terminal Disclaimer is not an admission or acquiescence by, nor shall act as an estoppel, upon the Applicants on the merits of the rejection.

In view of the above arguments and Terminal Disclaimer filed herewith, Applicants submit that claims 1-44, 60-67, and 81-91 are in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested and allowance of claims 1-44, 60-67, and 81-91 is kindly solicited.

Respectfully submitted,

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